page 3, line 5 (quantifying expression of gene products), page 4, line 17 (expression of abnormal levels of protein encoded by the nucleic acid molecules) and page 33, line 29 (determining expression of cancer associated antigen nucleic acids). No new matter has been added.

Rejections Under 35 U.S.C. 112, First Paragraph

The Examiner has maintained the rejection to claims 1, 2, 117-120 and 127 under 35 U.S.C. 112, first paragraph "...as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." The Examiner maintains the specification does not adequately describe the nucleic acids of NA Group 1 or fragments thereof. Although the Examiner notes that the Applicants have adequately described the nucleic acid sequences of SOX2, SOX1, ZIC2, SOX3 and SOX21, the Examiner argues that the specification does not adequately describe what deletions, additions and/or substitutions would code for cancer associated antigen precursors or fragments thereof as one of skill is not able to envision the structure and/or sequence of such molecules.

Applicants have amended claim 1 to overcome the rejection. The nucleic acid molecules encompassed by claim 1, as amended, include molecules which hybridize under stringent conditions to molecules with the nucleic acid sequence selected from the group consisting of SEQ ID NOs:3-17 which code for a cancer associated antigen precursor, degenerate nucleic acid molecules and complements thereof.

The Applicants maintain that one of skill in the relevant art is able to envision the nucleic acid molecules encompassed by the amended claim. The claimed methods use nucleic acid molecules that are set forth in detail throughout the specification. The specific attributes of these nucleic acid molecules, i.e., molecules that hybridize under specific high stringency conditions, degenerate molecules and complementary molecules are described, for example, on pages 16-18. Therefore, based on the teachings provided in the specification, the Applicants maintain that the claimed invention as a whole is adequately described.

While Applicants understand the Examiner's reliance on the recent biotechnology-related case law of written description, Applicants believe that there are several important distinctions between the facts of the cited cases and the facts of this instant application that compel conclusions opposite to those reached by the court.

First, in the recited cases, the sequences being claimed were not based on any sequence recitation at all, or the claimed sequences had no structured relation to the disclosed sequences. For example, in the Lilly case, there was "No sequence information indicating which nucleotides constitute human [insulin] cDNA appears in the patent, as appears for rat cDNA in Example 5 of the patent." University of California v. Eli Lilly 119 F.3d 1559, 43 USPQ 2d 1398 (Fed. Cir. 1997). Other factual situations in the cited cases similarly lacked any sequence disclosure related to the claimed invention.

In contrast, the present application provides an explicit recitation of sequences and further describes a set of physical parameters (stringent hybridization to the recited sequences) that circumscribe a set of related nucleic acid molecules that can be used in the diagnostic method claims. This disclosure is far more than that provided by the applicants in the recited case law. Unlike the situation in the Fiers v. Revel case, Applicants have provided more than "a mere statement that [the sequences in the claims are] part of the invention and a potential method of isolating" the sequences. Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Applicants contend that the disclosure is clearly sufficient for one of ordinary skill in the art to recognize that Applicants invented what is now claimed.

Second, the cited case law relates to the written description of claims directed to nucleic acid sequences. The cases did not specifically decide the proper standard for written description of claims drawn to methods for using certain nucleic acid sequences. As such, the generic standard of written description, enunciated in Vas-Cath v. Mahurkar, applies: an applicant must convey to one of ordinary skill in the art that the applicant was in possession of the invention as claimed. Vas-Cath v. Mahurkar 935 F.2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991). Applicants remind the Examiner that this test requires the evaluation of the level of skill of one of ordinary skill in the art, because in art with high skill levels (including the present one), persons of ordinary skill require fewer identifying characteristics to provide them with an understanding that an inventor was in possession of an invention. The Vas-Cath court stated that an adequate description of the invention required that the inventor "recount his invention in such detail that his future claims can be determined to be encompassed within his original creation." Vas-Cath, 935 F.2d at 1561, 19 USPQ2d at 1115, quoting Rengo Co. v. Molins Mach. Co., 657 F.2d 535, 551, 211 USPQ 303, 321 (3d Cir. 1981).

The disclosed sequences provide a central principle around which the genus is formed. The genus, in essence, is a group of nucleic acid molecules that are structurally very similar, and partially identical, to the recited sequences. The set of physical properties that describes the relationship between members of the genus is the stringent hybridization recited in the claim. Thus, hybridization is not a "potential method for isolating" the members of the genus; rather, stringent hybridization conditions (which are well known in the art) are a border that circumscribes the members of the genus. In combination with the recited nucleotide sequences, the stringent hybridization conditions describe with certainty a genus of nucleic acid molecules that can be used in the claimed methods. One of ordinary skill in the art can determine if a particular nucleic acid molecule is within the claimed invention by determining if that nucleic acid molecule would hybridize to one of the recited sequences under stringent hybridization conditions. Accordingly, one of ordinary skill in the art, upon reading the specification and claims, would recognize that Applicants were in possession of the invention as claimed, including the use of nucleic acid molecules that hybridize under stringent hybridization conditions to the recited nucleotide sequences. Therefore, Applicants maintain that the specification does contain an adequate written description of the claimed invention.

Based on the foregoing, Applicants respectfully request the Examiner withdraw the rejection of the claims under 35 U.S.C. 112, first paragraph.

Rejections Under 35 U.S.C. 112, Second Paragraph

The Examiner has rejected claims 1, 2 and 117-127 under 35 U.S.C. 112, second paragraph "...as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention." The Examiner maintains that in order to diagnose a disorder, one of skill would be required to differentiate between normal and cancerous tissues that express the nucleic acid molecules of the claims. The Examiner concludes that a mere interaction is not sufficient to determine a disorder as some of the antigens were found to be expressed in normal tissues.

The Applicants have amended claim 1 to recite that the diagnosis of a disorder may be made by determining the presence of interaction or a level of interaction between the agent and the nucleic acid molecule. The Applicants maintain that one of skill in the art would be able to recognize that the mere interaction between the agent and nucleic acid molecule is sufficient for

the determination of a disorder for those nucleic acid molecules not expressed in the normal tissue counterpart of the cancerous tissue, as is well described in the specification. This would be true, for example, for SOX1, SOX3 and SOX 21. This would also be applicable to ZIC2 in non-brain and non-testis cancers as well as for SOX2 in some cancerous tissues. Because the expression of these genes is provided in the specification, the methods cannot be indefinite, as it will be clear to one of ordinary skill in the art that the claimed methods are applicable for detecting (a) any expression of the genes in cancers where there is no normal expression, and (b) increased expression in tissues that do normally express the genes. The Applicants further maintain that one of skill would be able to recognize the necessity of assessing the differential expression of nucleic acid molecules expressed in both the normal tissue and its cancerous tissue counterpart, as these are normal, well-defined aspects of diagnostic methods, but are not required for the patentability of the instant claims.

In light of the amendment of independent claim 1 and the level of skill in the art, Applicants respectfully request the Examiner withdraw the rejection of the claims under 35 U.S.C. 112, second paragraph.

Summary

Applicants respectfully request reconsideration of the claims in view of the amendments and reasoned statements made above. If the Examiner wishes to advance the prosecution in any way, or if the amendment is defective or unclear, then the Examiner is invited to telephone the undersigned at the telephone number listed below.

Respectfully submitted,

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MARKED-UP SPECIFICATION

One also can search for class I and class II motifs using computer algorithms. For example, computer programs for predicting potential CTL epitopes based on known class I motifs has been described (*see, e.g.*, Parker at al, *J. Immunol.* 152:163, 1994; D'Amaro et al., *Human Immunol.* 43:13-18, 1995; Drijfhoust et al., *Human Immunol.* 43:1-12, 1995). Computer programs for predicting potential T cell epitopes based on known class II motifs has also been described (*see, e.g* Sturniolo et al., *Nat Biotechnol* 17(6):555-61, 1999). HLA binding predictions can conveniently be made using an algorithm available via the Internet on the National Institutes of Health World Wide Web site[at URL http://bimas.dcrt.nih.gov]. See also the website of: SYFPEITHI: An Internet Database for MHC Ligands and Peptide Motifs[(access via http://www.uni-tuebingen.de/uni/kxi/ or http://134.2.96.221/scripts/hlaserver.dll/EpPredict.htm]. Methods for determining HLA class II peptides and making substitutions thereto are also known (e.g. Strominger and Wucherpfennig (PCT/US96/03182)).

MARKED-UP CLAIMS

1. (Twice Amended) A method of diagnosing a disorder characterized by expression of a human cancer associated antigen precursor coded for by a nucleic acid molecule, comprising:

contacting a biological sample isolated from a subject with an agent that binds under stringent hybridization conditions to the nucleic acid molecule, an expression product thereof, or a fragment of an expression product thereof complexed with an HLA molecule, wherein the nucleic acid molecule is [a NA Group 1 nucleic acid molecule] selected from the group consisting of (1) nucleic acid molecules which hybridize under stringent conditions to a molecule consisting of a nucleic acid sequence selected from the group consisting of SEQ ID NOs:3-17 and which code for a cancer associated antigen precursor, (b) nucleic acid molecules that differ from the nucleic acid molecules of (a) in codon sequence due to the degeneracy of the genetic code, and (c) complements of (a) or (b), and

determining the presence or level of interaction between the agent and the nucleic acid molecule or the expression product as a determination of the disorder.